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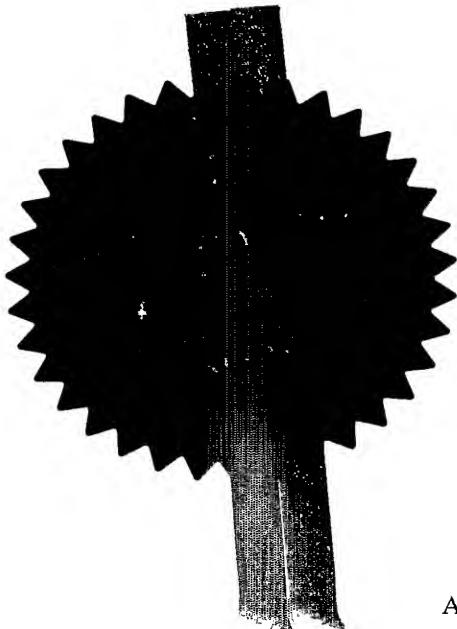
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Signed

Dated 7 April 2005



1/77

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## Request for grant of a patent

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an explanatory leaflet from the Patent Office to help you fill in  
this form)

1. Your reference

REP07786GB

20AUG04 EP20215-7 D02690  
P01/7700 0.00-0418556.7 CHEQUE

2. Patent application number

(The Patent Office will fill this part in)

0418556.7

3. Full name, address and postcode of the or of  
each applicant (underline all surnames)

Arakis Ltd.  
Chesterford Research Park  
Little Chesterford  
Saffron Walden  
Essex  
CB10 1LX

Patents ADP number (if you know it)

8306128001

If the applicant is a corporate body, give the  
country/state of its incorporation

United Kingdom

4. Title of the invention

The treatment of pain

5. Name of your agent (if you have one)

Gill Jennings &amp; Every

"Address for service" in the United Kingdom  
to which all correspondence should be sent  
(including the postcode)

Broadgate House  
7 Eldon Street  
London  
EC2M 7LH

Patents ADP number (if you know it)

745002

6. Priority: Complete this section if you are  
declaring priority from one or more earlier  
patent applications, filed in the last 12 months.

Country

Priority application number  
(if you know it)Date of filing  
(day / month / year)7. Divisionals, etc: Complete this section only if  
this application is a divisional application or  
resulted from an entitlement dispute (see note f)Number of earlier UK application  
(day / month / year)8. Is a Patents Form 7/77 (Statement of  
inventorship and of right to grant of a patent)  
required in support of this request?

YES

Answer YES if:

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an  
applicant, or
- c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

# Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form

Description	3
Claim(s)	2
Abstract	
Drawing(s)	

cf

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for a preliminary examination and search (Patents Form 9/77)

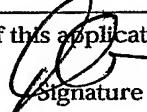
Request for a substantive examination (Patents Form 10/77)

NO

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application.

For the applicant  
Gill Jennings & Every

  
Signature

Date 19 August 2004

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

PERRY, Robert Edward  
020 7377 1377

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## Notes

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## The treatment of pain

### Field of the invention

This invention relates to the treatment of pain

### Background

5 Phenyl substituted beta-amino alcohols (I) are known to have antihypertensive, vasodilator, sympathomimetic, bronchodilator or cardiotonic activity through agonism and antagonism at alpha and beta adrenoceptors.

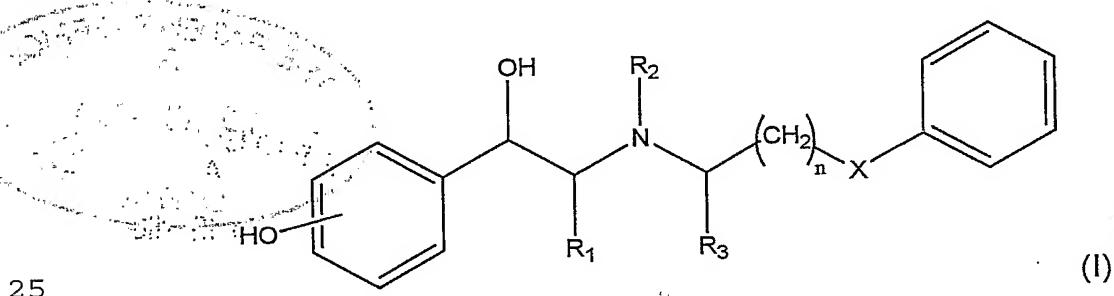
10 In GB Application No. 0406016.6 we have reported the cytokine modulating activity of these compounds, which is not dependant on the alpha and beta agonist or antagonist activity.

### Summary of invention

15 Surprisingly it has been found that phenyl substituted beta-amino alcohols (I) work at reducing pain in pain conditions where cytokines are involved. According to the present invention, pain such as acute, chronic or neuropathic pain (including, but not limited to, pain associated with cancer, surgery, arthritis, dental surgery, painful neuropathies, trauma, musculo-skeletal injury or disease, and visceral diseases) and migraine headache in mammals, can be treated by the use of phenyl substituted beta-amino alcohols 20 (I).

### Description of Preferred Embodiments

Phenyl substituted beta-amino alcohols refer to compounds of general formula (I)



Wherein:

R<sub>1</sub> may be H or Me

R<sub>2</sub> may be H or alkyl and can be part of a ring with R<sub>3</sub>

R<sub>3</sub> may be H or Me or CH<sub>2</sub> (when forming part of a ring with R<sub>2</sub>)

5 n=0-2

X may be CH<sub>2</sub> or O

The two phenyl groups may be optionally substituted with OH, OMe, halogen, NHCHO, NHSO<sub>2</sub>Me, CONH<sub>2</sub>, SOMe

10 It is understood that the invention refers to salts, e.g. the hydrochloride, metabolites and pro-drugs thereof, as well as any diastereomers and enantiomers of (I).

Compounds of formula (I) include bufeniode, butopamine, denopamine, fenoterol, formoterol, isoxuprine, labetalol, medroxalol, mesuprine, nylidrin, protokylol, ritodrine, salmefamol, sulfinalol.

15 According to another aspect of the invention the preferred diastereomer or enantiomer of (I) has little or no activity at the α or β adrenoceptors. This activity may be determined by use of the appropriate *in vitro* assay.

20 The compounds of formula (I) according to the invention exhibit analgesic activity in animal models. The activity of these compounds may be determined by use of the appropriate *in vivo* assay.

25 This invention also relates to a method of treatment for patients (including man and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from chronic, acute or neuropathic pain; and more specifically, a method of treatment involving the administration of the analgesic of formula (I) as the active constituent.

Accordingly, the compounds of formula (I) can be used among other things in the treatment of pain conditions such as acute and chronic pain (as well as, but not limited to, pain associated with cancer, surgery, arthritis, dental surgery, trauma, musculo-skeletal injury or disease, visceral diseases) and 30 migraine headache. Additionally the painful conditions can be neuropathic (post-herpetic neuralgia, diabetic neuropathy, drug induced neuropathy, HIV

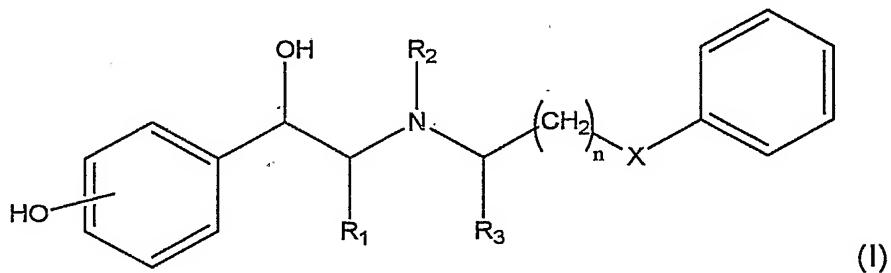
mediated neuropathy, sympathetic reflex dystrophy or causalgia, fibromyalgia, myofacial pain, entrapment neuropathy, phantom limb pain, trigeminal neuralgia. Neuropathic conditions include central pain related to stroke, multiple sclerosis, spinal cord injury, arachnoiditis, neoplasms, syringomyelia, 5 Parkinson's and epilepsy.

It will often be advantageous to use compounds of formula (I) in combination with another drug used for pain therapy. Such another drug may be an opiate or a non-opiate such as baclofen. Especially for the treatment of neuropathic pain, coadministration with gabapentin is preferred. Other 10 compounds that may be used include acetaminophen, a non-steroidal anti-inflammatory drug, a narcotic analgesic, a local anaesthetic, an NMDA antagonist, a neuroleptic agent, an anti-convulsant, an anti-spasmodic, an anti-depressant or a muscle relaxant.

Any suitable route of administration can be used. For example, any of 15 oral, topical, parenteral, ocular, rectal, vaginal, inhalation, buccal, sublingual and intranasal delivery routes may be suitable. The dose of the active agent will depend on the nature and degree of the condition, the age and condition of the patient and other factors known to those skilled in the art. A typical dose is 10-100 mg given one to three times per day.

## Claims

1. Use of a compound for the manufacture of a medicament for use in the treatment of a pain condition wherein the compound is of formula I



5

wherein

R<sub>1</sub> is H or Me;

R<sub>2</sub> is H or C<sub>1-6</sub> alkyl or is part of a ring with R<sub>3</sub>;

R<sub>3</sub> is H, Me or (when forming part of a ring with R<sub>2</sub>) CH<sub>2</sub>;

10 n=0-2;

X is CH<sub>2</sub> or O; and

the two benzene rings are each optionally substituted with OH, OMe, halogen, NHCHO, NHSO<sub>2</sub>Me, CONH<sub>2</sub> or SOMe; or a salt thereof.

15

2. Use according to claim 1, wherein the compound is selected from bufeniode, butopamine, denopamine, fenoterol, formoterol, isoxuprine, labetalol, medroxalol, mesuprine, nylidrin, protokylol, ritodrine, salmefamol, and sulfinalol.

20 3. Use according to claim 1 or claim 2, wherein the pain condition is chronic pain such as chronic back pain, malignant pain, chronic headache (including migraine and cluster headaches) or arthritic pain.

4. Use according to claim 1 or claim 2, wherein the pain condition is acute pain such as post-operative pain, post-traumatic pain or acute disease induced pain.
5. Use according to claim 1 or claim 2, wherein the pain condition is neuropathic pain.
6. Use according to any preceding claim, for use in combination with at least one other agent selected from a non-steroidal anti-inflammatory drug, a narcotic analgesic, a local anaesthetic, an NMDA antagonist, a neuroleptic, an anti-convulsant, an anti-spasmodic, an anti-depressant and a muscle relaxant.